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Cortisol and Fatty Liver: Researchers Find Cause of Severe Metabolic Disorders

Scientists of the German Cancer Research Center discover how the cortisol receptor can disrupt the lipid metabolism in the liver

A healthy body stores fat in the form of so-called triglycerides in specialized fatty tissue as an energy reserve. Under certain conditions the delicate balance of the lipid metabolism gets out of control and fat is accumulated in the liver, leading to the dreaded fatty liver. This increases the risk of many metabolic diseases, such as the metabolic syndrome known as “deadly quartet”. This combination of fatty liver, obesity, diabetes and hypertension is regarded as the primary cause of life-threatening vascular events such as myocardial infarction and stroke.

It was still unknown which conditions cause the body to deposit fat in the liver. However, scientists knew that the body’s own glucocorticoid hormones such as cortisol promote the development of fatty liver. This can be observed, for example, in a condition known as Cushing syndrome. Cortisol levels in affected patients are permanently raised – often caused by malignant tumors. This, in turn, leads to high blood sugar levels and patients frequently develop fatty liver. Long-term cortisone therapies such as those used for treating chronic inflammatory diseases such as asthma also cause the triglyceride level in the liver to rise to dangerous levels. Dr. Stephan Herzig, head of the Junior Research Group “Molecular Metabolic Control” at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), and his team have now published the mechanism by which the body’s own glucocorticoid hormones contribute to this disruption of the lipid metabolism.

The researchers in Herzig’s team specifically switched off the cortisol receptor in the livers of mice, thus blocking the hormone’s effect. As a result, the triglyceride level in the livers of the experimental animals dropped considerably. Investigations have revealed that, in the absence of the cortisol receptor, large amounts of the HES1 protein are produced in the livers of these animals. HES1 activates a number of enzymes that break down fat and, thus, counteracts fat accumulation in the liver. If, on other hand, normal mice are treated with cortisol, their HES1 levels in the liver drops, while triglyceride levels rise. Further experiments have shown that the cortisol receptor in this newly found metabolic pathway act directly on a switch of the HES1 gene and, thus, switches it off completely.

“We have discovered a key mechanism here that plays a crucial role in many pathologic metabolic disorders,” explains Stephan Herzig. “It has been obvious for some time that there is an association between the body’s own cortisol or therapeutically administered cortisone and the development of fatty liver. Now we also know what the interconnections look like at a molecular level.”

Ulrike Lemke, Anja Krones-Herzig, Mauricio Berriel Diaz, Prachiti Narvekar, Anja Ziegler, Alexandros Vegiopoulos, Andrew Cato, Sebastian Bohl, Ursula Klingmüller, Robert A. Screaton, Karin Müller-Decker, Sander Kersten and Stephan Herzig: The Glucocorticoid Receptor Controls Hepatic Dyslipidemia through Hes1. Cell Metabolism 2008, DOI: 10.1016/j.cmet.2008.08.001

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